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March 7, 2005
Date of Signature

Our Case No. 9793/73
RDGmbH Ref. 18931-US/IR (5181/0Q/US)
RDC Ref. BMID 9903 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Johann Karl et al.

Serial No. 09/890,442

Filing Date: January 31, 2002

For: Assay for the Detection of N-Terminal proBNP

Examiner James Leslie Grun, Ph.D.

Group Art Unit No. 1641

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

By the filing of this Appeal Brief in accordance with 37 CFR § 41.37, Appellants respectfully request reconsideration by the Board of Patent Appeals and Interferences in the above-identified patent application.

The Office date of receipt of Appellants's Notice of Appeal is October 7, 2004, which is the date from which the time period for filing the present Appeal Brief is

calculated (MPEP 1206). The fee set forth in 37 CFR § 41.20(b)(2) is enclosed herewith.

Real Party in Interest

The real party in interest is Roche Diagnostics GmbH, an organization having a place of business in Mannheim, Germany.

Related Appeals and Interferences

Currently, there are no pending appeals or interferences related to the present appeal.

Status of Claims

1. Claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119, and 129-141 are present and active in the application (assuming entry of Appellants's concomitantly filed After Final Amendment under 37 CFR § 1.116, which cancels previously pending claims 29-37, 47-55, 65-73, 84-92, 102-110, and 120-128).

2. Claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119, and 129-141 have been finally rejected.

3. The rejections of claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119, and 129-141 are being appealed.

Status of Amendments

In order to simplify issues for appeal, Appellants file herewith an After Final Amendment under 37 CFR § 1.116 canceling claims 29-37, 47-55, 65-73, 84-92, 102-110, and 120-128 and clarifying claim 140.

Appellants await notification from the Examiner as to whether this concomitantly filed amendment will be entered. However, inasmuch as this amendment fully complies with 37 CFR §§ 1.116 and 41.33(b)(1), Appellants have assumed that the amendment will be entered for purposes of determining the status of claims in this Appeal Brief.

Summary of Claimed Subject Matter

There are ten (10) independent claims involved in this appeal: claims 20, 129, 130, 132, 136, 137, 138, 139, 140, and 141.

1. Independent claim 20 recites a method of identifying N-terminal proBNP in a sample that involves detecting a complex of N-terminal proBNP, a first antibody, and a second antibody, wherein the first and second antibodies are specific to different epitopes of the N-terminal proBNP (e.g., specification, page 1, lines 1-2; page 6, lines 4-13; page 7, lines 1-20; page 9, lines 5-6; etc.), and wherein a lower detection limit for the N-terminal proBNP is less than 1 fmol/ml of sample (e.g., specification, page 10, lines 6-13; pages 22-23, Example 4; page 23, lines 17-19; etc.).

2. Independent claim 129 recites a method of producing antibodies against N-terminal proBNP that involves immunizing an organism with recombinant N-terminal proBNP and isolating antibodies from the organism (e.g., specification, page 12, lines 2-11; page 13, lines 11-22; page 16, Example 2, lines 1-15; page 18, Example 3, lines 7-21; etc.).

3. Independent claim 130 recites an antibody against recombinant N-terminal proBNP (e.g., specification, page 12, lines 12-21; etc.).

4. Independent claim 132 recites an antibody against N-terminal proBNP produced by immunizing an organism with recombinant N-terminal proBNP (e.g., specification, page 12, lines 10-13; page 13, lines 1-10; etc.).

5. Independent claim 136 recites an antibody against N-terminal proBNP produced by immunizing an organism with recombinant N-terminal proBNP (e.g., specification, page 12, lines 10-13; page 13, lines 1-10; etc.), wherein the antibody is equivalent to one produced by cell lines M 10.1.11, M 13.4.14, or a combination thereof (e.g., specification, page 13, lines 7-10; etc.).

6. Independent claim 137 recites cell line M 10.1.11 (e.g., specification, page 13, lines 1-6; Example 3, page 18, line 4 to page 19, line 4; etc.).

7. Independent claim 138 recites cell line M 13.4.14 (e.g., specification, page 13, lines 1-6; Example 3, page 18, line 4 to page 19, line 4; etc.).

8. Independent claim 139 recites a method of producing polyclonal antibodies against N-terminal proBNP that involves immunizing an organism with

recombinant N-terminal proBNP, isolating antibodies from the organism, screening the antibodies for reactive isotopes, and purifying the antibodies by immunosorption (e.g., specification, page 13, lines 13-17; Example 2, page 16, line 1 to page 17, line 13; etc.).

9. Independent claim 140 recites a method of producing monoclonal antibodies against N-terminal proBNP that involves immunizing an organism with recombinant N-terminal proBNP, fusing cells obtained from the organism with myeloma cells to produce hybrid cells that produce monoclonal antibodies, and selecting clones of the hybrid cell according to reactivity with native N-terminal proBNP in different pools of patient sera (e.g., specification, page 13, lines 18-22; Example 3, page 18, line 4 to page 20, line 26; etc.).

10. Independent claim 141 recites a method of identifying N-terminal proBNP in a sample that involves simultaneously binding first and second antibodies to N-terminal proBNP (e.g., specification, page 6, lines 9-13; etc.), and detecting a complex of the N-terminal proBNP, the first antibody, and the second antibody, wherein the first and second antibodies are specific to different epitopes of the N-terminal proBNP (e.g., specification, page 1, lines 1-2; page 6, lines 4-13; page 7, lines 1-20; page 9, lines 5-6; etc.), and wherein a lower detection limit for the N-terminal proBNP is less than 1 fmol/ml of sample (e.g., specification, page 10, lines 6-13; pages 22-23, Example 4; page 23, lines 17-19; etc.).

Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection which Appellants wish the Board to review on Appeal are the following:

1. The rejection of claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119, and 129-141 under 35 U.S.C. § 112, first paragraph (written description rejection).

2. The rejection of claims 134-138 under 35 U.S.C. § 112, first paragraph (compliance with deposit rules rejection).

3. The rejection of claims 22, 40, 58, 77, 95, 113, 136, 140, and 141 under 35 U.S.C. § 112, second paragraph (indefiniteness rejection).

4. The rejection of claims 130-131 under 35 U.S.C. § 101 (non-statutory subject matter rejection).

5. The rejection of claims 129-133, 136, and 139 under 35 U.S.C. § 102(b) as being anticipated by *Hall* (United States Patent No. 5,786,163).

6. The rejection of claims 20-28, 38-46, 56-64, 129-133, 136, and 139-141 as being unpatentable over *Hall* in view of *Hunt et al.* (*Clin. Endocrinol.* **1997**, *47*, 287).

7. The rejection of claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119, 129-133, 136, and 139-141 as being unpatentable over *Hall* in view of *Hunt et al.* and further in view of *Seilhamer et al.* (WO 89/12069) and *Sudoh et al.* (*Biochem. Biophys. Res. Comm.* **1989**, *159*, 1427).

Argument

1. Argument with Respect to Ground of Rejection No. 1

Reversal of the Examiner's rejection of claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119, and 129-141 under 35 U.S.C. § 112, first paragraph (written description rejection) is respectfully requested for the reasons set forth below.

Appellants respectfully traverse the Examiner's assertion in the Final Office Action (page 3, line 2) that "one would not know which sequences or structures were part of the invention" based on the definition of N-terminal proBNP provided in the specification.

The "sequences or structures" encompassed by the phrase "N-terminal proBNP" would have been abundantly clear to one of ordinary skill in the art in view of the following definition and the context in which it was given:

> Since the method according to the invention does not allow to differentiate between N-terminal proBNP, proBNP and parent peptides (breakdown products) NT-proBNP means in the following all peptides identified in the test procedure, in particular the known N-terminal proBNP (1-76). (specification, page 6, third full paragraph)

As described in the specification (e.g., page 6, second full paragraph), the claimed methods provide detection of native N-terminal proBNP in a sample; in cases in which the detected molecule remains intact, the detected molecule corresponds to N-terminal amino acids 1-76 of proBNP (e.g., specification, paragraph bridging pages 3 and 4). However, as further explained (e.g., page 6, second full paragraph; page 11, first full paragraph), the peptidic material that binds to the antibodies in the claimed methods may correspond to a

partially proteolytically digested fragment of N-terminal proBNP (i.e., a subset of the 76 amino acids) or to uncleaved proBNP (amino acids 1-76 still attached to amino acids 77-108). In reality, however, uncleaved proBNP (1-108) is barely released from the heart muscle into the blood and, moreover, is subject to a very quick breakdown (e.g., specification, page 4, lines 2-6). Thus, unlike the amino acids 1-76 (i.e., N-terminal proBNP), proBNP itself (1-108) is hardly detected in a blood sample.

Since the claimed methods may not differentiate between native N-terminal proBNP (1-76), and breakdown products containing a subset of amino acids 1-76, Appellants have defined the phrase "N-terminal proBNP" as it is used in reference to materials detected in a test procedure to include these above-described related peptides.

There is no inconsistency between the definition of N-terminal proBNP provided on page 6 of the specification—a definition provided in the context of the material or materials potentially identified in the sample—and the statement on page 10 that "N-terminal proBNP is the N-terminal part consisting of the amino acids 1-76." In view of the definition on page 6, one of ordinary skill in the art would readily recognize that the 76 amino acid entity referred to on page 10 refers to native and/or uncleaved material, which is merely a subset of a larger group of related peptides that may be identified by methods in accordance with the claimed invention and which are encompassed by the phrase "N-terminal proBNP" as defined by Appellants.

Appellants respectfully submit that the definition provided on page 6 of the specification fully conforms with MPEP 2111.01, which states that "[a]ny special meaning assigned to a term 'must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention.' *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998)." Appellants respectfully submit that there is no ambiguity associated with the definition of N-terminal proBNP provided in the specification and that one of ordinary skill in the art would readily understand what is meant from the context.

For at least the reasons set forth above, Appellants respectfully submit that the sequences or structures encompassed by the phrase "N-terminal proBNP" as defined in

the specification would be abundantly clear to those of ordinary skill in the art. Accordingly, reversal of this ground of rejection is respectfully requested.

2. Argument with Respect to Ground of Rejection No. 2

Reversal of the Examiner's rejection of claims 134-138 under 35 U.S.C. § 112, first paragraph (compliance with deposit rules rejection) is respectfully requested for the reasons set forth below.

As described in the specification (e.g., page 13, first full paragraph), monoclonal antibodies produced by the cell lines MAB M 10.1.1 and MAB M 13.4.14 were deposited and received on the 26th of January 1999 with the DSMZ GmbH in Braunschweig, Germany. In accordance with MPEP 2405, the DSMZ (i.e., Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) is recognized as an international depository under the Budapest Treaty.

As further evidence of compliance with the deposit rules and 37 CFR §§ 1.801-1.809, Appellants attach herewith Exhibits I and II. Exhibit I contains copies of Form DSMZ-BP/4 and Form DSMZ-BP/9 acknowledging receipt by the International Depositary Authority of cell line M 10.1.11. Exhibit II contains copies of Form DSMZ-BP/4 and Form DSMZ-BP/9 acknowledging receipt by the International Depositary Authority of cell line M 13.4.14. The documents contained in Exhibits I and II were originally provided to the Office at the time of filing and form part of the official record for this application.

Inasmuch as the specification already contains evidence of a deposit in compliance with 37 CFR §§ 1.801-1.809, and proof of the deposits has already been filed with the Office, Appellants respectfully submit that the claimed invention is fully enabled and that the written description is entirely adequate. Accordingly, reversal of this ground of rejection is respectfully requested.

3. Argument with Respect to Ground of Rejection No. 3

Reversal of the Examiner's rejection of claims 40, 58, 77, 95, 113, 136, 140, and 141 under 35 U.S.C. § 112, second paragraph (indefiniteness rejection) is respectfully requested for the reasons set forth below.

(a) Rejection of Claims 22, 40, 58, 77, 95, 113, and 141

The meaning of the claim recitation "bind simultaneously" would have been abundantly clear to one of ordinary skill in the art in view of the description in the specification.

The phrase "bind simultaneously" does not necessarily imply that the first and second antibodies must be added simultaneously, as is evident from the description in the specification. For example, in the method described on page 7 of the specification (lines 6-16), the first and second antibodies are not introduced simultaneously but rather in a stepwise fashion (steps a) and b), respectively).

Thus, the phrase "bind simultaneously" instead refers to the ability of the first and second antibodies to be bound to N-terminal proBNP at the same time by virtue of being bound to different epitopes. This meaning of the phrase is clear from the description in the specification. For example, the specification states that "[t]he distance of the two epitopes on the molecule must be large enough so that the simultaneous binding of the antibodies to the N-terminal proBNP is possible without reservation; if not, no sandwich complex can be built" (page 9, lines 6-8, emphasis added). Similarly, the specification states that "the epitopes are localized in a manner enabling both antibodies to bind at the same time and not to be too far away from each other" (page 6, second full paragraph, emphasis added).

For at least the reasons set forth above, Appellants respectfully submit that the meaning of the phrase "bind simultaneously" would be clear to one of ordinary skill in the art based on the description in the specification, and that this phrase does not render the rejected claims indefinite. Accordingly, reversal of this ground of rejection is respectfully requested.

(b) Rejection of Claim 136

The meaning of the claim recitation "the antibody ... is equivalent" would have been abundantly clear to one of ordinary skill in the art in view of the description in the specification.

The meaning of the claim recitation "the antibody ... is equivalent" has been clearly defined in the specification. For example, the specification states that "[a] further subject

matter of the invention are antibodies which are like those of the cell lines M 10.1.11 and M 13.4.14 produced in an equivalent way and suitable for specifically binding to N-terminal proBNP." The specification further states that "[t]he expression 'antibodies produced in an equivalent way' means that the antibodies are obtained by immunization with recombinant N-terminal proBNP" (page 13, second full paragraph, emphasis added).

For at least the reasons set forth above, Appellants respectfully submit that the meaning of the phrase "the antibody .. is equivalent" would be clear to one of ordinary skill in the art based on the description in the specification, and that this phrase does not render the rejected claims indefinite. Accordingly, reversal of this ground of rejection is respectfully requested.

(c) Rejection of Claim 140

The interrelationship of acts in method claim 140 was clarified in the accompanying After Final Amendment under 37 CFR § 1.116. When entered, this amendment is believed to render the rejection of claim 140 moot. However, in the event the rejection of claim 140 is maintained, Appellants respectfully submit that the interrelationship of acts in this claim as presently written would be abundantly clear to one of ordinary skill in the art. As presently written, claim 140 recites that the monoclonal antibodies are produced by hybrid cells, and that the hybrid cells to be cloned are selected according to their reactivity with native N-terminal proBNP. Thus, if claim 140 stands rejected by the time Appellant's appeal is considered by the Board, reversal of this rejection is respectfully requested.

4. Argument with Respect to Ground of Rejection No. 4

Reversal of the Examiner's rejection of claims 130-131 under 35 U.S.C. § 101 is respectfully requested for the reasons set forth below.

Claims 130-131 are directed to antibodies against recombinant N-terminal proBNP. At a minimum, the recombinant techniques employed in the production of recombinant N-terminal proBNP reflect the "hand of man," as does the production of antibodies from this recombinant material, which would further involve immunization of an organism with the "man made" recombinant material and the isolation and purification of the antibodies

produced by the organism (e.g., specification, Example 2, pages 16-17; Example 3, pages 18-19).

Inasmuch as the claimed antibodies are produced and isolated by procedures involving the "hand of man," Appellants respectfully submit that the claimed antibodies represent statutory subject matter. Accordingly, reversal of this ground of rejection is respectfully requested.

5. Argument with Respect to Ground of Rejection No. 5

Reversal of the Examiner's rejection of claims 129-133, 136, and 139 under 35 U.S.C. § 102(b) as being anticipated by *Hall* is respectfully requested for the reasons set forth below.

MPEP 2131 states that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

However, *Hall* fails to teach, either expressly or inherently, or to suggest each and every element recited in rejected independent claims 129, 130, 132, 136, and 139. Moreover, and in view of 35 U.S.C. § 112, fourth paragraph, which states that "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers," *Hall* also fails to teach or suggest each and every element recited in dependent claims 131 and 133. At a minimum, *Hall* does not teach or suggest "recombinant N-terminal proBNP," an element that is recited in each of independent claims 129, 130, 132, 136, and 139. Indeed, as noted in the specification (e.g., page 11, line 3), "[n]o recombinant N-terminal proBNP [was] hitherto known in the state of the art" prior to Appellants's disclosure.

Independent claims 129 and 139 are directed to a method of producing antibodies against N-terminal proBNP and require "immunizing an organism with recombinant N-terminal proBNP" (emphasis added). Independent claims 130, 132, and 136 are directed to "antibodies against recombinant N-terminal proBNP" (emphasis added).

The method of producing antibodies described in *Hall* is based on immunizations with peptide fragments of N-terminal proBNP—not with recombinant N-terminal proBNP,

as required by the claimed invention. There is no teaching or suggestion in *Hall* of any desirability or advantage of immunizing an organism with recombinant N-terminal proBNP as opposed to peptide fragments thereof. However, as described in the specification (e.g., page 21), antibodies obtained via peptide immunizations exhibit substantially differently affinities for native N-terminal proBNP as compared to antibodies obtained via recombinant N-terminal proBNP immunizations in accordance with the claimed invention. This difference is strikingly evident from a consideration of the data in Example 3 of the specification, which shows that antibodies obtained from peptide immunization (i.e., by a method analogous to that reported in *Hall*) have little or no reactivity with native N-terminal proBNP (e.g., page 21, Table 1). In contrast, antibodies obtained from immunization with recombinant N-terminal proBNP in accordance with the claimed invention react very strongly with native N-terminal proBNP (e.g., page 21, Table 2). This distinction is quite important because in reality, the material that is to be detected in a sample corresponds to native N-terminal proBNP.

The shortcomings of the peptide immunization methods used in *Hall* are further described in Appellants's specification as follows:

> [*Hall*] describes an immunological method of identifying N-terminal proBNP and the antibodies used for it. To obtain these antibodies single synthetically produced peptides from the sequence of N-terminal proBNP are used here. The production of antibodies by means of peptide immunization is possible in principle but the affinity regarding the whole molecule generally is too low to reach the necessary sensitivity in a test procedure. In addition, there is a danger that when using peptides the antibodies obtained can for example identify the C-terminus of the peptide and can therefore only bind to this fragment of the whole molecule. From this results that these antibodies cannot bind to the whole molecule or only to a low extent. In [*Hall*] polyclonal antibodies against one single peptide derived from the N-terminal proBNP are produced. It is shown that the antibodies produced bind to the immunization peptide (amino acids 47-64) in the competitive test format. It is however not shown that the antibodies are able to bind to native N-terminal proBNP as a whole molecule in a sample. Additionally, the sandwich test described in [*Hall*] in a sample cannot be performed as described since there was no appropriate standard material and no antibodies against two different epitopes. (specification, page 4, lines 8-22)

Inasmuch as *Hall* fails to teach or suggest immunizing an organism with recombinant N-terminal proBNP, as required by independent claims 129 and 139, and fails to teach or suggest antibodies against recombinant N-terminal proBNP, as required by independent claims 130, 132, and 136, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this reference. Accordingly, reversal of this ground of rejection is respectfully requested.

6. Argument with Respect to Ground of Rejection No. 6

Reversal of the Examiner's rejection of claims 20-28, 38-46, 56-64, 129-133, 136, and 139-141 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* is respectfully requested for the reasons set forth below.

(a) Claims 20-28, 38-46, 56-64 and 141

MPEP 2142 states that "[to] establish a *prima facie* case of obviousness ... the prior art reference ... must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

However, the combination of *Hall* and *Hunt et al.* fails to teach, either expressly or inherently, each and every element recited in rejected independent claims 20 and 141, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claims. Moreover, and in view of 35 U.S.C. § 112, fourth paragraph, which states that "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers," the combination of references also fails to teach, either expressly or inherently, each and every element recited in dependent claims 21-28, 38-46, and 56-64, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected dependent claims. At a minimum, the combination of references fails to teach or suggest "a lower detection limit for the N-terminal proBNP ... less than 1 fmol/ml of the sample," an element that is recited in each of rejected independent claims 20 and 141.

Hall describes an N-terminal proBNP antibody and immunoassay for its use. *Hall* contains no teaching or suggestion of "a lower detection limit for the N-terminal proBNP ... less than 1 fmol/ml of the sample," as required by the claimed invention. Whereas in the claimed invention, antibodies are produced against recombinant N-terminal proBNP, the immunoassays described in *Hall* are performed using antibodies obtained by immunization of peptide fragments of N-terminal pro-BNP (e.g., amino acid fragments 1-21, 22-46, and 47-64) (e.g., col. 4, lines 30-41). The production of antibodies by means of peptide immunization results in antibodies that have poor affinity for the whole N-terminal proBNP molecule, which results in test procedures having significantly lower sensitivities than that required by the claimed invention (e.g., specification, page 4, first full paragraph; page 5, first full paragraph).

The claimed invention provides methods for identifying N-terminal proBNP via sandwich-type assays using first and second antibodies, and has a lower detection limit for N-terminal proBNP that is less than 1 fmol/ml of sample. In contrast, the examples described in *Hall* are limited to competitive assays having significantly lower sensitivity. For example, as described in the specification (e.g., page 5, first full paragraph), the competitive test performed in WO 93/24531 (the counterpart PCT publication to the cited *Hall* U.S. Patent) results in a lower detection limit of approximately 250 fmol/ml—about 250 times larger than that required by the claimed invention. This higher detection limit is neither sufficient for the differentiation of healthy individuals and patients suffering from heart failure nor for a differentiated classification of patient samples into the severity degrees of heart failure, as described in the specification (e.g., page 5, first full paragraph).

The claimed lower detection limit required by the claimed invention, which is neither taught nor suggested in *Hall*, is likewise neither taught nor suggested in *Hunt et al.* *Hunt et al.* describes that N-terminal proBNP (1-76) may be a more discerning marker of cardiac impairment than BNP-32 (77-108) (e.g., page 287, col. 2, last paragraph) and does not teach or suggest sandwich-type assays of the claimed invention. Moreover, *Hunt et al.* contains no teaching or suggestion of "a lower detection limit for the N-terminal proBNP ... less than 1 fmol/ml of the sample," as required by the claimed invention. In contrast, *Hunt et al.* states that the detection limit

for the competitive assay of N-terminal proBNP described therein is about 5.2 pmol/l, which corresponds to about 5.2 fmol/ml (e.g., paragraph bridging pages 289-290). This detection limit is more than five times higher than that required by the claimed invention. The most specific and sensitive assay for N-terminal proBNP described in *Hunt et al.* has a lower detection limit of 1.3 pmol/l (i.e., 1.3 fmol/ml), which still exceeds the maximum value of the lower detection limit required by the claimed invention (page 293, second column, first full paragraph). Moreover, the sensitivities achieved in *Hunt et al.* require that complex extraction procedures be performed on the plasma samples prior to measurement (page 288, second column, first full paragraph). As described in the specification (e.g., page 5, second full paragraph), these complex extraction procedures may lead to the destruction of the analyte and errors in measurement.

Thus, inasmuch as the combination of *Hall* and *Hunt et al.* does not teach or suggest "a lower detection limit for the N-terminal proBNP ... less than 1 fmol/ml of the sample," as required by independent claims 20 and 141, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, reversal of this ground of rejection is respectfully requested.

(b) Claims 129-133, 136, and 139-140

MPEP 2142 states that "[to] establish a *prima facie* case of obviousness ... the prior art reference ... must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

However, the combination of *Hall* and *Hunt et al.* fails to teach, either expressly or inherently, each and every element recited in rejected independent claims 129, 130, 132, 136, 139, and 140 and provides no teaching or suggestion as to the desirability of modifying the methods and antibodies described therein to include each and every element of the rejected independent claims. Moreover, and in view of 35 U.S.C. § 112, fourth paragraph, which states that "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers," the combination of references also fails to teach, either expressly or inherently, each and every element recited in dependent claims 131 and 133 , and provides no teaching or

suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected dependent claims. At a minimum, the combination of references fails to teach or suggest "recombinant N-terminal proBNP," an element that is recited in each of independent claims 129, 130, 132, 136, 139, and 140.

Independent claims 129, 139, and 140 are directed to a method of producing antibodies against N-terminal proBNP and require "immunizing an organism with recombinant N-terminal proBNP" (emphasis added). As noted above, the method of producing antibodies described in *Hall* is based on immunizations with peptide fragments of N-terminal proBNP—not with recombinant N-terminal proBNP, as required by the claimed invention. Similarly, the method of producing an antiserum described in *Hunt et al.* is based on immunization of rabbits with a peptide fragment of amino acids 1-13 of human proBNP—not with recombinant N-terminal proBNP, as required by the claimed invention (page 288, second column, first full paragraph). Thus, inasmuch as the combination of *Hall* and *Hunt et al.* does not teach or suggest immunizing an organism with recombinant N-terminal proBNP, as required by the claimed invention, Appellants respectfully submit that independent claims 129, 139, and 140 are neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, reversal of this ground of rejection is respectfully requested.

Independent claims 130, 132, and 136 are directed to antibodies against recombinant N-terminal proBNP. As noted above, the antibodies described in *Hall* are produced against peptide fragments of N-terminal proBNP—not against recombinant N-terminal proBNP, as required by the claimed invention. Similarly, as noted above, the antiserum described in *Hunt et al.* is based on immunization of rabbits with a peptide fragment of amino acids 1-13 of human proBNP—not with recombinant N-terminal proBNP, as required by the claimed invention. Inasmuch as the combination of *Hall* and *Hunt et al.* does not teach or suggest antibodies against recombinant N-terminal proBNP, as required by independent claims 130, 132, and 136, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, reversal of this ground of rejection is respectfully requested.

7. Argument with Respect to Ground of Rejection No. 7

Reversal of the Examiner's rejection of claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119, 129-133, 136, and 139-141 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* and further in view of *Seilhamer et al.* and *Sudoh et al.* is respectfully requested for the reasons set forth below.

(a) Claims 20-28, 38-46, 56-64, 75-83, 93-101, 111-119 and 141

MPEP 2142 states that "[to] establish a *prima facie* case of obviousness ... the prior art reference ... must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

However, the combination of *Hall*, *Hunt et al.*, *Seilhamer et al.* and *Sudoh et al* fails to teach, either expressly or inherently, each and every element recited in rejected independent claims 20 and 141, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claims. Moreover, and in view of 35 U.S.C. § 112, fourth paragraph, which states that "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers," the combination of references also fails to teach, either expressly or inherently, each and every element recited in dependent claims 21-28, 38-46, 56-64, 75-83, 93-101, and 111-119 and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected dependent claims. At a minimum, the combination of references fails to teach or suggest "a lower detection limit for the N-terminal proBNP ... less than 1 fmol/ml of the sample," an element that is recited in each of rejected independent claims 20 and 141.

As noted above, the claimed lower detection limit of "less than 1 fmol/ml of the sample" required by the claimed invention is neither taught nor suggested in *Hall* or *Hunt et al.* *Seilhamer et al.* describes recombinant techniques for the production of natriuretic peptides and likewise neither teaches nor suggests the claimed lower detection limit. *Sudoh et al.* describes cloning and sequence analysis of cDNA encoding a

precursor for human brain natriuretic peptide and likewise neither teaches nor suggests the claimed lower detection limit.

Inasmuch as the combination of *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* does not teach or suggest "a lower detection limit for the N-terminal proBNP ... less than 1 fmol/ml of the sample, as required by independent claims 20 and 141, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, reversal of this ground of rejection is respectfully requested.

(b) Claims 129-133, 136, and 139-140

MPEP 2142 states that "[to] establish a *prima facie* case of obviousness ... the prior art reference ... must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

However, the combination of *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* fails to teach, either expressly or inherently, each and every element recited in rejected independent claims 129, 130, 132, 136, 139, and 140 and provides no teaching or suggestion as to the desirability of modifying the methods and antibodies described therein to include each and every element of the rejected independent claims. Moreover, and in view of 35 U.S.C. § 112, fourth paragraph, which states that "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers," the combination of references also fails to teach, either expressly or inherently, each and every element recited in dependent claims 131 and 133. At a minimum, the combination of references fails to teach or suggest "recombinant N-terminal proBNP," an element that is recited in each of independent claims 129, 130, 132, 136, 139, and 140.

Independent claims 129 and 139 are directed to a method of producing antibodies against N-terminal proBNP and require "immunizing an organism with recombinant N-terminal proBNP" (emphasis added). However, none of the applied references teaches or suggests recombinant N-terminal proBNP (i.e., a recombinant sequence corresponding to the 76 amino acids that constitute native N-terminal proBNP. As noted above, neither *Hall* nor *Hunt et al.* teaches or suggests immunizing an organism with recombinant N-terminal

proBNP, as required by the claimed invention. This deficiency is not remedied by either of the additional cited references. *Seilhamer et al.* describes a very long cDNA sequence of 1507 amino acids encoding porcine brain natriuretic peptide (e.g., Figure 1) and describes specific brain natriuretic peptides including porcine brain natriuretic peptide (pBNP; page 3) and a 6 amino acid N-terminal extended form of proBNP (e.g., page 4). However, *Seilhamer et al.* is completely silent with respect to the 76 amino acid N-terminal proBNP recited in the claimed methods. Moreover, although *Seilhamer et al.* carefully describes which portion of the sequence should be used to encode the 26 amino acid porcine brain natriuretic peptide (i.e., residues 660-723 and 1276-1289 inclusive; page 8), it neither teaches or suggests a recombinant version of the 76 amino acid peptide corresponding to native N-terminal proBNP required by the claimed methods, nor does it teach or suggest which portions of the 1507 amino acid cDNA sequence described therein should be selected in order to prepare such a recombinant N-terminal proBNP. *Sudoh et al.* is likewise silent with respect to the 76 amino acid N-terminal proBNP and contains no teaching or suggestion of the recombinant N-terminal proBNP required by the claimed methods. Inasmuch as the combination of *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* does not teach or suggest a recombinant N-terminal proBNP (1-76) as required by independent claims 129, 130, 132, 136, 139 and 140, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, reversal of this ground of rejection is respectfully requested.

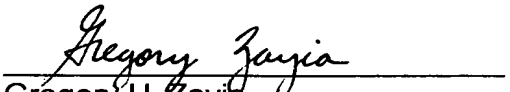
Independent claims 130, 132, 136, and 140 are directed to antibodies against recombinant N-terminal proBNP. As noted above, *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* are silent with respect to recombinant N-terminal proBNP corresponding to the 76 amino acid sequence required by the claimed invention. As a result, and not surprisingly, none of the applied references teaches or suggests antibodies against recombinant N-terminal proBNP. Inasmuch as the combination of *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* does not teach or suggest antibodies against recombinant N-terminal proBNP, as required by independent claims 130, 132, 136, and 140, Appellants respectfully submit that the claimed invention is neither anticipated by

nor would have been obvious in view of this combination of references. Accordingly, reversal of this ground of rejection is respectfully requested.

Conclusion

In conclusion, Appellants respectfully submit that the seven grounds of rejection raised by the Examiner have been overcome for at least the reasons set forth above. Accordingly, reversal of all grounds of rejection is respectfully requested.

Respectfully submitted,



Gregory H. Zayia
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Claims Appendix

20. A method of identifying N-terminal proBNP in a sample comprising:

detecting a complex of the N-terminal proBNP, a first antibody, and a second antibody; wherein

a lower detection limit for the N-terminal proBNP is less than 1 fmol/ml of the sample;

the first antibody is specific to a first epitope of the N-terminal proBNP;

the second antibody is specific to a second epitope of the N-terminal proBNP; and

the first epitope and the second epitope are different.

21. The method of claim 20, wherein at least one of the first and the second antibodies comprises a label, and wherein the method further comprises detecting a signal emitted from the label.

22. The method of claim 20 wherein the first and the second antibodies bind simultaneously to the N-terminal proBNP.

23. The method of claim 20 wherein the detecting is performed by a heterogeneous test procedure.

24. The method of claim 21 wherein the detecting is performed by a heterogeneous test procedure.

25. The method of claim 22 wherein the detecting is performed by a heterogeneous test procedure.

26. The method of claim 23 wherein the test procedure involves a sandwich assay.

27. The method of claim 24 wherein the test procedure involves a sandwich assay.

28. The method of claim 25 wherein the test procedure involves a sandwich assay.

38. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 20; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

39. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 21; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

40. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 22; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

41. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 23; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

42. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 24; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

43. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 25; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

44. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 26; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

45. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 27; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

46. A method of differentiating a sample taken from a healthy patient and a sample taken from a patient with a type of heart failure, comprising:

identifying an amount of N-terminal proBNP in a sample under study with the method of claim 28; and

correlating the amount of N-terminal proBNP identified in the sample under study with a level of N-terminal proBNP characteristic of a healthy patient or a patient with a type of heart failure;

wherein the type of heart failure is selected from the group consisting of NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV.

56. The method of claim 38 wherein the type of heart failure is NYHA Class I.

57. The method of claim 39 wherein the type of heart failure is NYHA Class I.

58. The method of claim 40 wherein the type of heart failure is NYHA Class I.

59. The method of claim 41 wherein the type of heart failure is NYHA Class I.

60. The method of claim 42 wherein the type of heart failure is NYHA Class I.

61. The method of claim 43 wherein the type of heart failure is NYHA Class I.

62. The method of claim 44 wherein the type of heart failure is NYHA Class I.

63. The method of claim 45 wherein the type of heart failure is NYHA Class I.

64. The method of claim 46 wherein the type of heart failure is NYHA Class I.

75. The method of claim 20 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

76. The method of claim 21 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

77. The method of claim 22 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

78. The method of claim 23 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

79. The method of claim 24 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

80. The method of claim 25 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

81. The method of claim 26 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

82. The method of claim 27 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

83. The method of claim 28 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

93. The method of claim 38 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

94. The method of claim 39 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

95. The method of claim 40 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

96. The method of claim 41 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

97. The method of claim 42 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

98. The method of claim 43 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

99. The method of claim 44 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

100. The method of claim 45 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

101. The method of claim 46 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

111. The method of claim 56 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

112. The method of claim 57 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

113. The method of claim 58 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

114. The method of claim 59 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

115. The method of claim 60 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

116. The method of claim 61 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

117. The method of claim 62 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

118. The method of claim 63 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

119. The method of claim 64 further comprising quantifying the N-terminal proBNP identified in the sample against a standard comprised of recombinant N-terminal proBNP.

129. A method of producing antibodies against N-terminal proBNP comprising:

immunizing an organism with recombinant N-terminal proBNP, such that the organism produces antibodies; and

isolating the antibodies from the organism.

130. An antibody against recombinant N-terminal proBNP.

131. The antibody of claim 130 wherein the antibody specifically binds N-terminal proBNP in a range between amino acids 10 to 66.

132. An antibody against recombinant N-terminal proBNP produced by immunizing an organism with recombinant N-terminal proBNP.

133. The antibody of claim 132 wherein the antibody specifically binds N-terminal proBNP in a range between amino acids 10 to 66.

134. The antibody of claim 130 produced by a cell line selected from the group consisting of M 10.1.11, M 13.4.14, and a combination thereof.

135. The antibody of claim 131 produced by a cell line selected from the group consisting of M 10.1.11, M 13.4.14, and a combination thereof.

136. An antibody against recombinant N-terminal proBNP produced by immunizing an organism with recombinant N-terminal proBNP, wherein the antibody thus produced is equivalent to an antibody against recombinant N-terminal proBNP produced by a cell line selected from the group consisting of M 10.1.11, M 13.4.14, and a combination thereof.

137. Cell line M 10.1.11.

138. Cell line M 13.4.14.

139. A method of producing polyclonal antibodies against recombinant N-terminal proBNP comprising:

immunizing an organism with recombinant N-terminal proBNP;
isolating the antibodies from the organism;
screening the antibodies for reactive epitopes; and
purifying the antibodies by immunosorption.

140. A method of producing monoclonal antibodies against recombinant N-terminal proBNP comprising:

immunizing an organism with recombinant N-terminal proBNP;

fusing cells obtained from the organism with myeloma cells to produce hybrid cells wherein the hybrid cells produce monoclonal antibodies; and

selecting clones of the hybrid cells according to reactivity with native N-terminal proBNP in different pools of patient sera.

141. A method of identifying N-terminal proBNP in a sample comprising:

binding a first antibody to the N-terminal proBNP;

binding a second antibody to the N-terminal proBNP; and

detecting a complex of the N-terminal proBNP, ~~a~~ the first antibody, and ~~a~~ the second antibody; wherein

a lower detection limit for the N-terminal proBNP is less than 1 fmol/ml of the sample;

the first antibody is specific to a first epitope of the N-terminal proBNP;

the second antibody is specific to a second epitope of the N-terminal proBNP;

the first antibody and the second antibody bind simultaneously to the N-terminal proBNP; and

the first epitope and the second epitope are different.

Evidence Appendix

Exhibit I contains copies of Form DSMZ-BP/4 and Form DSMZ-BP/9 acknowledging receipt by the International Depositary Authority of cell line M 10.1.11.

Exhibit II contains copies of Form DSMZ-BP/4 and Form DSMZ-BP/9 acknowledging receipt by the International Depositary Authority of cell line M 13.4.14.

The documents contained in Exhibits I and II were originally provided to the Office at the time of initial filing and have already been entered into the official record. Scans of these documents are contained in the PAIR system's Image File Wrapper for this application under the Document Description heading "Various IB Documents and Papers Submitted with the 371 Application such as the ISR and IPER: 112 Page(s)."

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

Roche Diagnostics GmbH
Sandhofer Str. 116

68305 Mannheim

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: MAK<proBNP>M 10.1.11	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM ACC2386

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

( ) a scientific description
( ) a proposed taxonomic designation

(Mark with a cross where applicable).

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1999-01-26 (Date of the original deposit)[1].

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weiss Date: 1999-02-11

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

Form DSMZ-BP/4 (sole page) 0196

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

Roche Diagnostics GmbH
Sandhofer Str. 116

68305 Mannheim

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Roche Diagnostics GmbH Sandhofer Str. 116 Address: 68305 Mannheim	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM ACC2386 Date of the deposit or the transfer[1]: 1999-01-26

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1999-01-27 [2].
On that date, the said microorganism was

(X)[3] viable

( )[3] no longer viable

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weiks Date: 1999-02-11

[1] Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
[2] In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
[3] Mark with a cross the applicable box.
[4] Fill in if the information has been requested and if the results of the test were negative.

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

Roche Diagnostics GmbH
Sandhofer Str. 116

68305 Mannheim

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: MAK<proBNP>M 13.4.14	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM ACC2387

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

( ) a scientific description
( ) a proposed taxonomic designation

(Mark with a cross where applicable).

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1999-01-26 (Date of the original deposit)[1].

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weiß Date: 1999-02-11

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

Form DSMZ-BP/4 (sole page) 0196

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

Roche Diagnostics GmbH
Sandhofer Str. 116

68305 Mannheim

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Roche Diagnostics GmbH Sandhofer Str. 116 Address: 68305 Mannheim	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM ACC2387 Date of the deposit or the transfer[1]: 1999-01-26

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1999-01-27 [2].
On that date, the said microorganism was

(X)[3] viable

( )[3] no longer viable

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name:	DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):
Address:	Mascheroder Weg 1b D-38124 Braunschweig	U. Weiß Date: 1999-02-11

[1] Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
[2] In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
[3] Mark with a cross the applicable box.
[4] Fill in if the information has been requested and if the results of the test were negative.

Form DSMZ-BP/9 (sole page) 0196